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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,126	ISACSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004 and 04 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 16-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 16-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/17/02 and 8/4/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed April 8, 2004 (herein after referred to as "the response") has been entered. Claims 1, 4, and 16-18 have been amended. Claims 2-3 and 5-15 have been cancelled. Claims 19-32 have been newly added.

Accordingly, Claims 1, 4, and 16-32 are pending in the instant application.

The drawing amendments filed August 4, 2004 are approved and the corrected drawing has been entered.

The objection to the declaration is withdrawn in view of the newly filed declaration of April 8, 2004.

The objection to the specification is withdrawn in view of the amendments to the specification.

The rejection of Claims 1-11 under 35 U.S.C. 102(e) is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 16-18 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended and newly added claims include new matter.

Claim 16 has been amended so that it now recites that the embryonic stem cells are administered in a "suspension of 50 to 50,000 cells per microliter" and newly added Claims 30-32 also recite this limitation. However, the specification does not recite this particular range. Applicants have not pointed to any support in the as-filed specification for this new range. The Examiner reviewed the entire specification, particularly page 11 and Example 13, beginning on page 35, and did not find support for the newly recited range.

Thus, the amended claims and newly added claims include new matter.

Enablement

Claims 1, 4, and 16-18 stand rejected and Claims 19-32 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action mailed 10/6/03, and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a human patient suffering from Parkinson's disease (PD) by various protocols. Although the preamble implies that the method will result in treatment of the disease, no particular treatment effect is achieved.

The claims now cover treating Parkinson's disease with either dopaminergic or serotonergic neurons. However, neither the prior art nor the instant specification teach that serotonergic neurons are useful in treating Parkinson's disease.

At pages 10-12 of the response, Applicants assert that genetic modification of human ES cells is enabled. Applicants argue that the Zwaka reference only suggests that the genetic modification of human ES cells is inefficient and that inefficiency is not an appropriate basis for a lack of enablement rejection.

Applicants further argue that the Zwaka reference does not suggest that electroporation of human ES cells is entirely unsuccessful. Applicants conclude that "for this reason alone, Zwaka proves that the instant specification enables the genetic modification of human ES cells." On the contrary, the instant specification does not teach transfecting human ES cells by electroporation, but rather teaches using adenovirus transduction for the genetic modification of ES cells (see Example 6). No results are provided for the adenovirus transduction experiments. Furthermore, the prior art does not enable adenovirus transduction of human ES cells. Thus, it is the role of the instant specification to provide an enabling disclosure for adenoviral transduction of human ES cells.

At page 12, paragraph 2 of the response, Applicants argue that the Eiges reference demonstrates that alternative techniques for genetic modification of human ES cells were available in the art. Applicants argue that electroporation can be useful for transfecting human ES cells because Figure 1 of Eiges et al. shows luciferase reporter gene activity when human ES cells were transfected by electroporation. Although very low levels of reporter gene activity were detected in cells transfected by electroporation, the reference also states that "human ES cells do not survive electroporation well" (p. 515, column 1, paragraph 1). Furthermore, the instant specification does not teach transfecting human ES cells by electroporation, but rather teaches using adenovirus transduction for the genetic modification of ES cells (see Example 6). Again, no results are provided for the adenovirus transduction experiments. Applicants further argue that Eiges demonstrates that transfection of human ES cells using FuGENE and ExGen 500 is successful. However, there is no evidence that the transduction method disclosed in the specification, i.e. adenovirus transduction, can be used successfully to obtain cell compositions, expressing the introduced nucleic acid, that are suitable compositions for therapeutic transplantation. Furthermore, since the specification does not disclose what level of transfection efficiency is needed to carry out the claimed method for producing a useful cell composition, suitable for therapeutic transplantation, it is not evident that high efficiency transfection is not needed. Likewise, it is not evident

that the transfection methods disclosed in the specification would provide even a low level of transfection. The specification does not show that low level transfection would be suitable for the differentiation protocol recited in the claims, nor does it show that cell compositions resulting from low level transfection would have the use asserted in the specification, which is for therapeutic transplantation. Furthermore, some of the claims require the transplantation of cells in which at least 90% of the cells are dopaminergic or serotonergic neurons (Claims 30-32). One of skill in the art would expect that high efficiency transfection protocols would be required to produce such cell populations. Thus, Applicants arguments are not commensurate in scope with the scope of the claims. Applicants arguments are based on the assumption that inefficient transfection protocols would be suitable to carry out the claimed protocols to achieve a therapeutic effect in a patient with Parkinson's disease. However, given the limited successes in the art of therapeutic transplantation for patients with Parkinson's disease, and the unpredictability in the art with regard to the particular types of cell compositions that are suitable for therapeutic transplantation, such an assumption is only speculative at best.

At page 12, paragraph 3 of the response, Applicants argue that Examples 2, 9, and 10 of the specification teach the transfection of murine ES cells with a vector encoding Nurr-1 using Lipofectamine according to the manufacturer's protocol. Applicants conclude that Eiges demonstrates that chemical transfection methods similar to the one used by Applicants can be successfully applied to human ES cells. This is not the case because the instant specification does not teach that human ES cells should be transfected using Lipofectamine, but rather provides specific guidance for transducing human ES cells with an adenoviral vector (see Example 6). There is no evidence at this time demonstrating that adenoviral vector can be used to transfect human ES cells to provide a significant population of dopaminergic neurons suitable for therapeutic transplantation to PD patients. Furthermore, Eiges had already demonstrated that Lipofectamine was a very inefficient method for transfecting human ES cells, thereby teaching away from the use of Lipofectamine-mediated transfection.

At page 12, paragraph 4 of the response, Applicants conclude that Zwaka and Eiges support rather than refute, Applicants' assertion that a skilled artisan would be able to genetically modify human ES cells using no more than routine experimentation. Applicants further note that Eiges was published on April 3, 2001, which is prior to the filing date of the instant application. Applicants conclude that the art cited proves that the specification, combined with techniques and reagents available at the time of filing, enables the genetic modification of human ES cells. While one of skill in the art could have potentially used the ExGen 500 transfection protocol to transfect human ES cells to develop cell compositions for transplantation according to the claimed invention, the specification teaches away from using such a transfection method because it specifically teaches that adenoviral vector transduction should be used to transfect human ES cells for the purpose of carrying out the claimed methods to develop cell compositions suitable for therapeutic transplantation. Since neither the specification nor the prior art teaches that adenoviral vector transduction of human ES cells is effective, particularly for the aim of generating cell compositions that have therapeutic potential in transplantation to PD patients, the initial step in producing appropriate cell compositions, i.e. transfecting human ES cells, clearly requires further experimentation. That reality is not in dispute here. However, given that numerous other parameters in the claimed method also require further experimentation to achieve the therapeutic result required, and further given the nature of the invention, broad scope of the claims, state of the art, lack of working examples, and limited teachings of the specification, when viewed as a whole, the nature and quantity of experimentation rises to the level of undue experimentation.

At pages 13-18 of the response, Applicants assert that the claimed invention does not encompass gene therapy. At pages 13-14, Applicants argue that their invention is not gene therapy because the claimed method is "cell therapy, not gene therapy, and it does not depend upon *in vivo* gene expression" (page 14, line 4). Contrary to Applicants' belief, the claimed method clearly encompasses *ex vivo* gene therapy, and Claims 16-18 are directed exclusively to *ex vivo* gene therapy. Thus, the methods of Claims

16-18 do require and depend upon *in vivo* gene expression, contrary to Applicants' statements. As stated in the previous Office Action "[t]he specification fails to teach an appropriate method for transferring a recombinant cell comprising a cell fate-inducing gene and expressing that gene at a level necessary to produce the desired therapeutic effect in a diseased animal, i.e. to produce replacement neurons at the critical locations" (page 4, lines 1-4). Claims 16-18 are specifically and exclusively directed to administering embryonic stem cells to a patient, "such that the cells form, in the patient, a population of cells in which at least 90% the cells are dopaminergic or serotonergic neurons." The embryonic stem cells may be transfected with either the Nurr-1 gene or the PTX-3 gene. The transfected cells are **not** differentiated *in vitro* prior to transplantation. Thus, the method clearly depends on *in vivo* gene expression, "to produce replacement neurons at the critical locations" as argued by the Examiner, contrary to Applicants' statements. Applicants conclude that "no guidance on *in vivo* gene expression is required." However, for the reasons discussed above, not only is *in vivo* gene expression required, but said gene expression must be sufficient to produce replacement neurons at the critical locations. Thus, guidance is clearly required.

At pages 14-16, Applicants assert that transplanted cells produce replacement neurons. Applicants argue that the claimed method involves transplanting neurons, rather than ES cells, and that enabling guidance is found in the prior art. This is simply not true, as the claims clearly encompass transplanting ES cells. Claims 16-18 are exclusively directed to the transplantation of ES cells. Thus, Applicants arguments are not commensurate in scope with the scope of the claims. With regard to Applicants arguments relating to prior art transplantation of dopaminergic neurons, the prior art methods do not involve developing cell compositions from human ES cells, but rather involve the use of primary cells isolated from fetal brain. Such cell compositions are distinct from the cell compositions being used here and the prior art has not been successful in developing cell compositions comprising human dopaminergic neurons from stem cells in culture such that said compositions are suitable for producing a

therapeutic effect in humans with Parkinson's disease. The development of appropriate **human** cell compositions is critical to production of a therapeutic effect and neither the instant specification nor the prior art provides specific guidance for producing such cell compositions from human ES cells.

At pages 16-18, Applicants assert that the instant specification provides sufficient teachings with regard to obtaining gene expression and performing cell transplantation. Applicants arguments hinge on experiments carried out using genetically modified mouse ES cells in transplantation to mice or rats. However, for the reasons discussed above, with regard to the genetic modification of human ES cells, results obtained with mouse ES cells are not predictive of results obtained with human ES cells. Given the unpredictability in the art, the skilled artisan would recognize that undue experimentation would be required to

At pages 18-19 of the response, Applicants argue that the examples of the specification, prior art (Lindvall, 1998), and the post-filing art (Kim et al., 2002) demonstrate that methods for cell transplantation to the human brain are well-developed. However, while it is acknowledged that one can readily inject cells into a specific site within the human brain and even detect cell survival post-transplantation, the **result** that may be achieved is **highly unpredictable** and is **often non-therapeutic** even when cells survive and engraft into the human brain. One of the critical elements is developing appropriate cell compositions for **therapeutic** transplantation. The instant specification does not provide sufficient guidance for obtaining such cell compositions, by routine experimentation, appropriate for production of a therapeutic effect in a PD patient, for reasons of record. The instant specification only teaches how to produce dopaminergic neurons from mouse ES cells, and mouse neurons are not suitable for transplantation into human patients.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of protocols covered by the claims, and the unpredictability for achieving a therapeutic effect upon the transplantation of human ES

cells or compositions developed from in vitro differentiation of human ES cells, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-29 are indefinite in their recitation of "recombinant embryonic stem" in part (a) of the claims because the word "cell" seems to be missing, thereby rendering the claims indefinite and confusing.

Claims 26-27 are indefinite in their recitation of "said stem cells or are transfected with a nucleic acid" because the phrase is not grammatically correct and it appears that something is missing or that something has been inadvertently inserted.

Claims 26-28 are indefinite in their recitation of "said stem cells" because the phrase lacks antecedent basis.

Claim 29 is indefinite in its recitation of "said recombinant cells" because the phrase lacks antecedent basis.

Claims 29-32 are indefinite in their recitation of "derived from" because the nature and number of derivative processes are not defined and therefore the metes and bounds of the claimed subject matter is not clearly set forth.

Claims 30-32 are indefinite in their recitation of "90% the cells" because the phrase is not grammatically correct.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER